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Examiner Name	M.S. Walicka
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ENCLOSURES *(check all that apply)*

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SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm or Individual	Lexicon Genetics Incorporated Lance K. Ishimoto Reg. No. 41,866
Signature	Reg No 40162, Peter G. Schrain
Date	September 29, 2003

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellant(s):	D. Wade Walke, *et al.*	Group Art Unit: 1652
Application No.:	09/833,782	Examiner: M.A. Walicka
Filed:	4/12/2001	
Title:	Novel Human Metalloprotease and Polynucleotides Encoding the Same	Atty. Docket No. LEX-0161-USA

APPEAL BRIEF

Mail Stop Appeal Brief
Commissioner for Patents
Alexandria, VA 22313

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APPEAL BRIEF

Sir:

Appellants hereby submit an original and two copies of this Appeal Brief to the Board of Patent Appeals and Interferences ("the Board") in response to the Final Office Action mailed January 24, 2003. The Notice of Appeal was timely submitted on April 24, 2003, and was received in the Patent and Trademark Office ("the Office") on April 29, 2003. This Appeal Brief is timely submitted in light of the concurrently filed Petition for an Extension of Time of three months to and including September 29, 2003 and authorization to deduct the fee as required under 37 C.F.R. § 1.17(a)(2) from Appellants' Representatives' deposit account. The Commissioner is also authorized to charge the fee for filing this Appeal Brief (**$160.00**), as required under 37 C.F.R. § 1.17(c), to Lexicon Genetics Incorporated Deposit Account No. 50-0892.

Appellants believe no fees in addition to the fee for filing the Appeal Brief and the fee for the extension of time are due in connection with this Appeal Brief. However, should any additional fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason related to this communication, the Commissioner is authorized to charge any underpayment or credit any overpayment to Lexicon Genetics Incorporated Deposit Account No. 50-0892.

I. REAL PARTY IN INTEREST

The real party in interest is the Assignee, Lexicon Genetics Incorporated, 8800 Technology Forest Place, The Woodlands, Texas, 77381.

II. RELATED APPEALS AND INTERFERENCES

Appellants know of no related appeals or interferences.

III. STATUS OF THE CLAIMS

The present application was filed on April 12, 2001, claiming the benefit of U.S. Provisional Application Number 60/196,319, which was filed on April 12, 2000, and included original claims 1-3. A First Official Action, was issued on January 18, 2002 ("the First Action"),

in which claims 1-3 were rejected under 35 U.S.C. § 101, as allegedly lacking patentable utility and under 35 U.S.C. § 112, first paragraph, as allegedly unusable by the skilled artisan due to the alleged lack of patentable utility, Claim 2 was also rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite, claim 3 was rejected under 35 U.S.C. § 102(b), as allegedly being anticipated. In a response to the First Official Action, submitted to the Office on April 18, 2002 ("response to the First Action"), Appellants amended claims 1-2 to further improve their clarity, and respectfully traversed the rejections of claim 1-3 under 35 U.S.C. § 101 and claim 1 under 35 U.S.C. § 112, first paragraph.

A Second Official Action, was issued on July 3, 2002 (the "Second Action"), in which rejection of claims 1-3 was maintained under 35 U.S.C. § 101 as allegedly lacking a patentable utility, claim 2 was rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite, rejection of claims 2-3 was also maintained under 35 U.S.C. § 112, first paragraph, as one skilled in the art clearly would not know how to make or use the invention. In a response to the Second Action, submitted on November 4, 2002 ("response to the Second Action"), Appellants amended claim 2 and added new claims 4-5 to better claim the invention.

A Third and Final Official Action, was issued on January 24, 2003 (the "Final Action"), in which rejection of claims 1-5 was maintained under 35 U.S.C. § 101 as allegedly lacking a patentable utility, claim 5 was rejected under 35 U.S.C. § 112, second paragraph, as being improperly dependent upon itself, rejection of claims 1-5 was also maintained under 35 U.S.C. § 112, first paragraph, as one skilled in the art clearly would not know how to use the invention. In a response to the Final Action, submitted on April 24, 2003 ("response to the Final Action") in which Appellants amended claim 5 to further improve its clarity.

An Advisory Action ("the Advisory Action") was mailed on May 16, 2003, the rejection of claim 5 was withdrawn under 35 U.S.C. § 112, second paragraph, however claims 1-5 remain rejected under 35 U.S.C. § 101 as allegedly lacking a patentable utility, andunder 35 U.S.C. § 112, first paragraph, as allegedly one skilled in the art clearly would not know how to use the invention. Therefore, claims 1-5 are the subject of this appeal. A copy of the appealed claims are included below in the Appendix (Section IX).

IV. STATUS OF THE AMENDMENTS

For the purposes of Appeal Appellants believe that no additional outstanding amendments exist.

V. SUMMARY OF THE INVENTION

The present invention relates to Appellants' discovery and identification of novel human sequences that encode a human metalloprotease, neurolysin. Also disclosed are the tissue expression pattern of these sequences (Page 3, lines 15-21) and naturally occurring polymorphisms that exist within these molecules (page 16, lines 21-28). The specification details a number of uses for the presently claimed sequences, including the detection and diagnosis of human diseases such as, *inter alia*, pain management and cardiac diseases wherein such molecules can act as drug targets (specification at page 1, lines 27-31). Appellants have used the methods described in the specification as filed (page 2 lines 11-32 and page 17, lines 17-23) to construct knockout mice which were used to biologically validate the assertions that the sequences of the present invention have utility as drug targets for human diseases, such as pain management and cardiac diseases (specification at page 1, lines 27-31). Additional uses for the sequences of the present invention include assessing temporal and tissue specific gene expression patterns (specification at page 6, line 24), particularly using a high throughput "chip" format (specification at page 5, line 30 through page 6, line 33), mapping the sequences to a specific region of a human chromosome and identifying protein encoding regions (specification at page 11, line 11-17), determining the genomic structure (specification at page 11, line 5-11), and in diagnostic assays such as forensic analysis, human population biology and paternity determinations (see, for example, the specification from page 11, line 5-17) wherein the sequences of the present invention are particularly useful as the specification identified polymorphisms (page 16, lines 21-28) that can be used in these assays. Thus, Appellants have described novel nucleic and amino acid sequences, their tissue expression pattern and naturally occurring polymorphisms (page 16, lines 21-28) that exist within the sequences of the present invention. The sequences of the present invention encode neurolysin, a protein of known function and Appellants have used methods described in the specification (page 2 lines 11-32 and

page 17, lines 17-23) as filed to biologically validate their assertions that the sequence of the present invention have utility as drug targets for human disease (specification at page 1, lines 27-31) among other utilities.

VI. ISSUES ON APPEAL

1. Do claims 1-5 lack a patentable utility?
2. Are claims 1-5 unusable by a skilled artisan due to a lack of patentable utility?

VII. GROUPING OF THE CLAIMS

For the purposes of the outstanding rejections under 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph, the claims will stand or fall together.

VIII. ARGUMENT

A. Do Claims 1-5 Lack a Patentable Utility?

The Final Action rejected and the Advisory Action maintained the rejection of claims 1-5 under 35 U.S.C. § 101, as allegedly lacking a patentable utility due to not being supported by either a specific and substantial utility or a well-established utility, this rejection is maintained in the Advisory Action.

Appellants have described novel nucleic and amino acid sequences, their tissue expression pattern and naturally occurring polymorphisms (page 16, lines 21-28) that exist within the sequences of the present invention. The sequences of the present invention encode neurolysin, a protein of known function and Appellants have used methods described in the specification (page 2 lines 11-32 and page 17, lines 17-23) as filed to biologically validate their assertions that the sequence of the present invention have utility as drug targets for human disease (specification at page 1, lines 27-31).

First, as set forth in the response to the First Action and the response to the Final Action, Appellants would like to invite the Board's attention to the fact that a sequence that is identical at the amino acid level over the entire length of the described sequence is present in the leading

scientific repository for biological sequence data (GenBank), and has been annotated by third party scientists *wholly unaffiliated with Appellants* as neurolysin (Homo sapiens) (GenBank accession number:CAC27329, alignment and GenBank report provided in **Exhibit A**). Therefore, it is clear that the amino acid sequence of SEQ ID NO:2 encodes human neurolysin.

Furthermore, Appellants would like to invite the Board's attention to the fact that GenBank Accession No. AJ300837 (alignment and GenBank report provided in **Exhibit B)** that describes a sequence annotated by others to be the mRNA for human neurolysin has a 99% identify with the nucleic acid sequence of SEQ ID NO: 1 (2113 of a total of 2115 bases present in SEQ ID NO: 1). These sequences have also been defined by third party scientists, wholly unaffiliated with Appellants, as encoding human neurolysin. Given this clear evidence that those skilled in the art have independently accepted the utility described in the present specification, there can be no question that Appellants' asserted utility for the described sequences is "credible." As such, the scientific evidence of identity at both the amino acid and nucleic acid levels clearly establishes that those of skill in the art would recognize the sequences of the present invention as human neurolysin, a protein with well known function. Therefore, Appellants have described a utility in full compliance with the provisions of 35 U.S.C. section 101, and the Examiner's rejection should be overturned.

Clearly evidence supports Appellants' assertions that the sequences of the present invention encode a novel human metalloprotease (specifically neurolysin, metallopeptidase M3) which has a well established utility that is recognized by those of skill in the art. Thus this situation parallels Example 10 of the PTO's Revised Interim Utility Guidelines Training Materials (pages 53-55), which establishes that a rejection under 35 U.S.C. § 101 as allegedly lacking a patentable utility and under 35 U.S.C. § 112, first paragraph as allegedly unusable by the skilled artisan due to the alleged lack of patentable utility, is not proper when there is no reason to doubt the asserted utility of a full length sequence (such as the presently claimed sequence) that has a similarity to a protein having a known function. In the Analysis portion of Example 10 it states that "Based on applicant's disclosure and the results of the PTO search, there is no reason to doubt the assertion that SEQ ID NO:2 encodes a DNA ligase . Further DNA ligases have a well-established use in the molecular biology art based on this class of proteins

ability to ligate DNA. .....Note that if there is a well-established utility already associated with the claimed invention, the utility need not be asserted in the specification as filed..... Thus the conclusion reached from this analysis is that a 35 U.S.C. § 101 and a 35 U.S.C. § 112 first paragraph, utility rejection should not be made."

The present case is similar to that presented in Example 10 of the Revised Interim Utility Guidelines Training Materials (pages 53-55). In the present case it is clear that the sequences of the present invention encode novel human metalloprotease (specifically neurolysin, metallopeptidase M3) . Neurolysin has well-established utility. According to the guidelines "Note that if there is a well-established utility already associated with the claimed invention, the utility need not be asserted in the specification as filed...Thus the conclusion reached from this analysis is that a 35 U.S.C. § 101 and a 35 U.S.C. § 112 first paragraph, utility rejection should not be made." Thus the rejection of the presently claimed invention under a 35 U.S.C. § 101 and a 35 U.S.C. § 112 first paragraph utility rejection should be overruled.

The biological significance and function of neurolysin and neurolysin like metalloproteases are well known to those of skill in the art. Evidence includes the publication cited as being allegedly prior art in the First Action under 35 U.S.C. § 102(b)(Kato, *et al.*, J. Biol Chem. 1997, 272, 15313-15322 (**Exhibit C**), in which their role in intracellular degradation of bioactive oligopeptides is described. Appellants submitted one of the many publications describing the activity of neurolysin, in the response to the Second Action in the form of an abstract of a review published by Shrimpton, Smith and Lew (Endocr. Rev. 2002 Oct; 23(5):647-64 (abstract included as **Exhibit D**) and additional evidence is provided by a publication by Norman, et al. (Am J Physiol Heart Circ Physiol. 2003: abstract provided as **Exhibit E**). Furthermore, in a section of the Final Action (at last line of page 3) the Examiner states "That are Chen *et al.* who demonstrated that human protein having the amino acid sequence as set forth in SEQ ID NO:2 is neurolysin and has specific, substantial, credible and well established utility." While Appellants disagree with the Examiner's conclusions regarding priority, because the Appellants' present application predates the disclosure of Chen, *et al.* and as stated in the response, that the only reasonable conclusion that one might draw from the information that the Examiner cited is that Chen *et al.* may have been the first to publish "that human protein having

the amino acid sequence as set forth in SEQ ID NO:2 is neurolysin and has specific, substantial, credible and well established utility." However from the Examiner's statements it would appear clear that neurolysin does indeed have specific, substantial, credible and well established utility.

However, in the Advisory Action the Examiner's position is that (page 7, lines 6-10) that "the fact that the third party scientists cloned the human neurolysin gene and disclosed the amino acid sequence of the enzyme after the Applicant filed the application does not change the fact that the protein of SEQ ID NO:2 encoded by DNA of SEQ ID NO:1 was disclosed by Applicants without asserting its function and utility." The Examiner then contradicts her prior statements "That are Chen *et al.* who demonstrated that human protein having the amino acid sequence as set forth in SEQ ID NO:2 is neurolysin and has specific, substantial, credible and well established utility" by taking the position that "even Chen et al. have thus far, not disclosed actual enzymatic activity of the protein set forth by SEQ ID NO:2 that is encoded by SEQ ID NO:1" (Advisory Action at page 7 lines 11-12) and presumably therefore, in spite of the many publications to the contrary, the utility of neurolysin remains to be established to the Examiner's satisfaction.

Included in a previous Action as a reason for the alleged lack of utility of the present invention is the statement that "Applicants themselves did not present any evidence that protein of SEQ ID NO:2 is able to cleavage neurotensin between residues Pro10 and Tyr11, and to bind angiotensin; the assays are easy to perform *in vitro.*" However, the ease of potential experimentation is not the issue, this emphasis is misplaced as it has long been established that "there is no statutory requirement for the disclosure of a specific example". *In re Gay*, 135 USPQ 311 (C.C.P.A. 1962). Appellants assertion of the stated utility is legally sufficient and should control the utility analysis unless the Examiner meets the burden of establishing the lack of utility by making evidence of record that conclusively refutes the Appellants asserted utility. In the Advisory Action the Examiner submits evidence that she feels does not support Appellants' assertions, however these submissions do not refute Appellants asserted utility.

Additionally, in the Response to the Final Action, Appellants submitted still further evidence of finding supporting the real world utility of the metalloprotease encoded by the sequences of the present invention as provided by Appellants findings involving the analysis of

transgenic "knockout" mice, in which the function of the gene encoding the sequences of the present invention were disrupted in embryonic stem cells (constructed as described in the specification at least on page 2, lines 11-32 and page 17, lines 17-23). Knockout mice prepared as described in the specification as filed were subject to a medical work-up using an integrated suite of medical diagnostic procedures designed to assess the function of the major organ systems in a mammalian subject. Disruption of the mouse gene of the present invention and thus elimination of the protein it encodes, resulted in an increased anxiety-like response, as manifested as a decreased sum center-to-total distance ratio and decreased center-to-total distance travel during all intervals tested when compared with their wild-type (+/+) littermates. Homozygous (-/-) mice, deficient in the gene and protein of the present invention, also demonstrated decreased paw flinching during phase II of a formalin pain assay, as compared to their wild-type (+/+) littermates, suggesting decreased sensitivity to pain. In Addition, female homozygous mutant mice exhibited a decreased heart rate when compared to gender-matched littermates and the historical mean. This clearly provides evidence that the nucleic acid and protein of the present invention have a biological function and the molecules of the present invention as well as agonists or antagonists directed at them can be used to diagnose and treat anxiety and pain disorders as well as cardiac disease (as stated in the specification at least at page 1, line 29), validated drug targets. Thus clearly the molecules of the present invention also have real world substantial and specific utility as having been identified as biologically validated drug targets using methods and identified for diseases and disorders asserted in the specification as filed.

Appellants invite the board to consider that those of skill in the art would readily recognize that molecules which share amino acid identity would also share function. Thus as SEQ ID NO:2 is 100% identical with a molecule recognized by those of skill in the art as neurolysin, SEQ ID NO:2 would also be recognized to have all the function, specific, substantial, credible and well established utility of neurolysin. The Advisory Action states (the last line of page 7-line 2 of page 8) that "Furthermore, the availability of post-filing date evidence of utility is irrelevant in the instant situation, where Applicants specification lacks any assertion of this utility." This position contradicts the position presented in Example 10 of the Revised

Interim Utility Guidelines Training Materials (pages 53-55), "Note that if there is a well-established utility already associated with the claimed invention, the utility need not be asserted in the specification as filed..."

In addition to contradicting Example 10 of the Guidelines, when the Advisory Action states (page 4 line 3-6) that Appellants describe only a protein sharing sequence similarity with mammalian neurolysin there is no assertion of function. Appellants disagree, as clearly those of skill in the art would readily recognize that functional properties are inherent to structural identity, identical structure begets identical function and thus, logically, identical utility.

Furthermore, Appellants have made several presentations which the Examiner has found non-persuasive as described in the Advisory Action. The Examiner does not appear to accept that Appellants assertion that the sequences of the present invention encode a novel human metalloprotease specifically metallopeptidase M3, neurolysin. In fact the Examiner does not appear to believe that such assertions were even made in the specification. Appellants respectfully submit to the Board that such assertions were made, among other locations, in the title of the original application "Novel Human Metalloprotease and Polynulcleotides Encoding the Same"; in the background information section of the specification, Section 2, where Appellants describe the activity of metalloproteases including neurolysin; and in the position taken by the Appellants throughout the specification and prosecution wherein the Appellants have identified the structural similarities between mammalian neurolysin proteins and the sequences of the present invention. Appellants have provided several pieces of evidence that those of skill in the art would find Appellants assertions credible. That evidence clearly shows that those of skill in the art, in no way affiliated with Appellants, when faced with the same information, would and did identify the sequences of the present invention as a metalloprotease, neurolysin and that those of skill in the art would readily recognize that functional properties are inherent to structural identity, identical structure begets identical function and thus, logically, identical utility.

Thus, the skilled artisan would readily appreciate the utilities asserted by Appellants' regarding the role of the proteins encoded by sequences of the present invention, including those associated with diseases that have been linked to the novel human metalloprotease, neurolysin.

Therefore, the present utility rejection must fail. According to the Examination Guidelines for the Utility Requirement, if the applicant has asserted that the claimed invention is useful for any particular purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, the Examiner should not impose a rejection based on lack of utility (66 Federal Register 1098, January 5, 2001).

The Advisory Action maintains that Appellants' assertions regarding the use of the presently claimed polynucleotides on DNA gene chips, based on the position that such a use would allegedly be generic. Further, these Actions seem to be requiring Appellants to identify the biological role of the nucleic acid or function of the protein encoded by the presently claimed polynucleotides before the present sequences can be used in gene chip applications that meet the requirements of § 101. Appellants respectfully point out that knowledge of the exact function or role of the presently claimed sequence is not required to track expression patterns using a DNA chip. As set forth in Appellants First Response, given the widespread utility of such "gene chip" methods using *public domain* gene sequence information, there can be little doubt that the use of the presently described *novel* sequences would have great utility in such DNA chip applications.

However, clearly given the extensive utility described above for the molecules encoded by the sequences of the present invention and evidence that the claimed sequences provide a specific marker of the gene encoding neurolysin and provide a unique identifier of the corresponding gene in the human genome. Such specific markers are targets for discovering drugs that are associated with human disorders and diseases such as, *inter alia*, pain management and cardiac disease (specification page 1, line 29). Thus, those skilled in the art would instantly recognize that the present nucleotide sequence would be an ideal, novel candidate for assessing gene expression using, for example, DNA chips, as the specification details at least on page 5, line 30 through page 6, line 33. Such "DNA chips" clearly have utility, as evidenced by hundreds of issued U.S. Patents, exemplified by U.S. Patent Nos. 5,445,934 (**Exhibit F**), 5,556,752 (**Exhibit G**), 5,744,305 (**Exhibit H**), as well as more recently issued U.S. Patent Nos. 5,837,832 (**Exhibit I**), 6,156,501 (**Exhibit J**) and 6,261,776 (**Exhibit K**).

The Board is further requested to consider that, given the huge expense of the drug discovery process, even negative information has great "real world" practical utility. Knowing

that a given gene is not expressed in medically relevant tissue provides an informative finding of great value to industry by allowing for the more efficient deployment of expensive drug discovery resources. Such practical considerations are equally applicable to the scientific community in general, in that time and resources are not wasted chasing what are essentially scientific dead-ends (from the perspective of medical relevance). Clearly, compositions that enhance the utility of such DNA gene chips, such as the presently claimed sequences encoding neurolysin which Appellants have shown are biologically validated drug targets for pain and cardiac disorder, among others, must in themselves be useful. Moreover, the presently described protein (neurolysin) provides uniquely specific sequence resources for identifying and quantifying full length transcripts that were encoded by the corresponding human genomic locus. Accordingly, there can be no question that the described sequences provide an exquisitely specific utility for analyzing gene expression.

The utility of the sequences of the present invention are further enhanced by the description in the specification of tissues expressing the sequences of the present invention (Page 3, lines 15-21) and the description of polymorphisms (page 16, lines 21-28). These teachings along with the above evidence that the molecules of the present invention encode a protein of known function and that Appellants have used methods described in the specification as filed to biologically validate their assertions that the sequence of the present invention have utility as drug targets for human disease, clearly demonstrate outstanding utility of the sequences in DNA chip expression analysis.

Still further, as only a small percentage of the genome (2-4%) actually encodes exons, which in turn encode amino acid sequences. Thus, not all human genomic DNA sequences are useful in such gene chip applications. This further discounts the Examiner's position that such uses are "generic". The present claims clearly meet the requirements of 35 U.S.C. § 101. It has been clearly established that a statement of utility in a specification must be accepted absent reasons why one skilled in the art would have reason to doubt the objective truth of such statement. *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA, 1974); *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA, 1971).

Additional evidence of the "real world" substantial utility of the present invention is further provided by the fact that there is an entire industry based on the use of gene sequences or fragments thereof in a gene chip format. Perhaps the most notable gene chip company is Affymetrix. However, there are many companies which have, at one time or another, concentrated on the use of gene sequences or fragments, in gene chip and non-gene chip formats, for example: Gene Logic, ABI-Perkin-Elmer, HySeq and Incyte. In addition, one such company, Rosetta Inpharmatics, was viewed to have such "real world" value that it was acquired by large pharmaceutical company, Merck & Co., for substantial sums of money (net equity value of the transaction was $620 million). The "real world" substantial industrial utility of gene sequences or fragments would, therefore, appear to be widespread and well established. Clearly, persons of skill in the art, as well as venture capitalists and investors, readily recognize the utility, both scientific and commercial, of genomic data in general, and specifically human genomic data. Billions of dollars have been invested in the human genome project, resulting in useful genomic data (see, *e.g.*, Venter *et al.*, 2001, Science *291*:1304; **Exhibit L**). The results have been a stunning success as the utility of human genomic data has been widely recognized as a great gift to humanity (see, *e.g.*, Jasny and Kennedy, 2001, Science *291*:1153; **Exhibit M**). Clearly, the usefulness of human genomic data, such as the presently claimed nucleic acid molecules, is substantial and credible (worthy of billions of dollars and the creation of numerous companies focused on such information) and well-established (the utility of human genomic information has been clearly understood for many years).

As a still further example of utility is the use of the present sequences in such diagnostic assays (at least at page 11, lines 5-17) as those associated with identification of paternity and forensic analysis, among others. The sequences of the present invention have particular utility as the application as filed identified several polymorphisms (page 16, lines 21-28). This is also not a case of a potential utility. Appellants respectfully submit that even in the worst case scenario, the described polymorphisms are each useful to distinguish 50% of the population (in other words, the marker being present in half of the population) and that the ability of a polymorphic marker to distinguish at least 50% of the population is an inherent feature of any polymorphic marker, and this feature is well understood by those of skill in the art. Appellants note that as a

matter of law, it is well settled that a patent need not disclose what is well known in the art. *In re Wands*, 8 USPQ 2d 1400 (Fed. Cir. 1988). Appellants support for Appellants' assertion of utility is provided by the fact that the skilled artisan would readily recognize and easily believe that the presently described polymorphic markers could be useful in forensic analysis. The fact that forensic biologists use polymorphic markers such as those described by Appellants every day provides more that ample support for the assertion that forensic biologists would also be able to use the specific polymorphic markers described by Appellants in the same fashion. Therefore, again it is clear that the sequences of the present invention have utility.

Given the physiologic activity and importance of neurolysin as known to those of skill in the art, those of skill in the art would readily appreciate the importance of tracking the expression of the genes encoding the described proteins, particularly due to the established role of neurolysin in human disorders such as such as pain management and cardiac diseases (specification at page 1, lines 27-31). The use of the claimed polypeptide in an array for screening purposes Appellants respectfully point out that nucleic acid sequences have the greatest specific utility in gene chip applications once the role of the sequence has been identified, as have tissues of interest, as in the present case. Once the role of the particular nucleic acid is known, the level of gene expression has and even greater significance. By identifying the physiological activity role of the claimed sequence, the claimed sequence has a far greater utility in gene chip applications that just any random piece of DNA. Appellants respectfully submit that **specific** utility, which is the proper standard for utility under 35 U.S.C. § 101, is distinct from the requirement for a **unique** utility, which is clearly an improper standard. As clearly stated by the Federal Circuit in *Carl Zeiss Stiftung v. Renishaw PLC*, 20 USPQ2d 1101 (Fed. Cir. 1991; "*Carl Zeiss*"):

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding a lack of utility." *Envirotech Corp. v. Al George, Inc.*, 221 USPQ 473, 480 (Fed. Cir. 1984)

Therefore, just because other nucleic acid sequences find utility in gene chip applications does not mean that the use of Appellants' sequence in gene chip applications is not a specific utility. Furthermore, the requirement for a unique utility is clearly not the standard adopted by the Patent

and Trademark Office. If every invention were required to have a unique utility, the Patent and Trademark Office would no longer be issuing patents on batteries, automobile tires, golf balls, golf clubs, and treatments for a variety of human diseases, such as cancer and bacterial or viral infections, just to name a few particular examples, because examples of each of these have already been described and patented. All batteries have the exact same utility - specifically, to provide power. All automobile tires have the exact same utility - specifically, for use on automobiles. All golf balls and golf clubs have the exact same utility - specifically, use in the game of golf. All cancer treatments have the exact same utility - specifically, to treat cancer. All anti-infectious agents have the exact same broader utility - specifically, to treat infections. However, only the briefest perusal of virtually any issue of the Official Gazette provides numerous examples of patents being granted on each of the above compositions every week. Furthermore, if a composition needed to be unique to be patented, the entire class and subclass system would be an effort in futility, as the class and subclass system serves solely to group such common inventions, which would not be required if each invention needed to have a unique utility. Thus, the present sequence clearly meets the requirements of 35 U.S.C. § 101.

Further evidence of utility of the presently claimed polynucleotide, although only one is needed to meet the requirements of 35 U.S.C. § 101 (*Raytheon v. Roper*, 220 USPQ 592 (Fed. Cir. 1983); *In re Gottlieb*, 140 USPQ 665 (CCPA 1964); *In re Malachowski*, 189 USPQ 432 (CCPA 1976); *Hoffman v. Klaus*, 9 USPQ2d 1657 (Bd. Pat. App. & Inter. 1988)), is the specific utility the present nucleotide sequence has in determining the genomic structure of the corresponding human chromosome (specification at page 11, lines 5-11) , for example mapping the protein encoding regions as described in the specification (page 11, lines 11-17) and evidenced below. Clearly, the present polynucleotide provides exquisite specificity in localizing the specific region of the human chromosome containing the gene encoding the given polynucleotide, a utility not shared by virtually any other nucleic acid sequence. In fact, it is this specificity that makes this particular sequence so useful. Early gene mapping techniques relied on methods such as Giemsa staining to identify regions of chromosomes. However, such techniques produced genetic maps with a resolution of only 5 to 10 megabases, far too low to be of much help in identifying specific genes involved in disease. The skilled artisan readily

appreciates the significant benefit afforded by markers that map a specific locus of the human genome, such as the present nucleic acid sequence.

Only a minor percentage of the genome actually encodes exons, which in turn encode amino acid sequences. The presently claimed polynucleotide sequence provides biologically validated empirical data (*e.g.,* showing which sequences are transcribed, spliced, and polyadenylated) that *specifically* defines that portion of the corresponding genomic locus that actually encodes exon sequence. Equally significant is that the claimed polynucleotide sequence defines how the encoded exons are actually spliced together to produce an active transcript (*i.e.*, the described sequences are useful for functionally defining exon splice-junctions). The Appellants respectfully submit that the practical scientific value of expressed, spliced, and polyadenylated mRNA sequences is readily apparent to those skilled in the relevant biological and biochemical arts. For further evidence supporting the Appellants' position, the Board is requested to review, for example, section 3 of Venter *et al.* (*supra at* pp. 1317-1321, including Fig. 11 at pp.1324-1325), which demonstrates the significance of expressed sequence information in the structural analysis of genomic data. The presently claimed polynucleotide sequence defines a biologically validated sequence that provides a unique and specific resource for mapping the genome essentially as described in the Venter *et al.* article.

As still further evidence supporting Appellants assertions of the specific utility of the sequences of the present invention in localizing the specific region of the human chromosome and identification of functionally active intron/exon splice junctions is the information provided in **Exhibit N**. This is the result of a blast analysis using SEQ ID NO:1 of the present invention when compared to the identified human genomic sequence. This result indicates that the sequence of the present invention is encoded by 13 exons spread non-contiguously along a region of human chromosome 5, which are contained within partially overlapping BAC clones, AC016643.6 and AC008958.7. Thus clearly one would not simply be able to identify the 13 protein encoding exons that make up the sequence of the present intention from within the large genomic sequence. Nor, would one be able to map the protein encoding regions identified specifically by the sequences of the present invention without knowing exactly what those specific sequences were.

In addition to the previously submitted Exhibits, demonstrating that the sequences of the present invention encode a metalloprotease, neurolysin. Genetic mapping of the sequences of the present invention maps to human chromosome 5, at the very same region as that to which neurolysin (NLN) has been mapped. Therefore, in addition to the clear sequence homology between molecules annotated as neurolysin, a metalloprotease, and the sequences of the present invention which have been evidenced. The sequences of the present invention and neurolysin (NLN), map to the same genetic locus, 5q12.2.

The question of utility is a straightforward one. As set forth by the Federal Circuit, "(t)he threshold of utility is not high: An invention is 'useful' under section 101 if it is capable of providing some identifiable benefit." *Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d 1700 (Fed. Cir. 1999) (citing *Brenner v. Manson*, 383 U.S. 519, 534 (1966)). Additionally, the Federal Circuit has stated that "(t)o violate § 101 the claimed device must be totally incapable of achieving a useful result." *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992), emphasis added. *Cross v. Iizuka* (224 USPQ 739 (Fed. Cir. 1985); "*Cross*") states "any utility of the claimed compounds is sufficient to satisfy 35 U.S.C. § 101". *Cross* at 748, emphasis added. Indeed, the Federal Circuit recently emphatically confirmed that "anything under the sun that is made by man" is patentable *(State Street Bank & Trust Co. v. Signature Financial Group Inc.*, 47 USPQ2d 1596, 1600 (Fed. Cir. 1998), citing the U.S. Supreme Court's decision in *Diamond vs. Chakrabarty*, 206 USPQ 193 (S.Ct. 1980)).

The legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible or believable. According to the Examination Guidelines for the Utility Requirement, if the applicant has asserted that the claimed invention is useful for any particular purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, the Examiner should not impose a rejection based on lack of utility (66 Federal Register 1098, January 5, 2001).

In *In re Brana,* (34 USPQ2d 1436 (Fed. Cir. 1995), "*Brana*"), the Federal Circuit admonished the P.T.O. for confusing "the requirements under the law for obtaining a patent with

the requirements for obtaining government approval to market a particular drug for human consumption". *Brana* at 1442. The Federal Circuit went on to state:

> At issue in this case is an important question of the legal constraints on patent office examination practice and policy. The question is, with regard to pharmaceutical inventions, what must the applicant provide regarding the practical utility or usefulness of the invention for which patent protection is sought. This is not a new issue; it is one which we would have thought had been settled by case law years ago.

Brana at 1439, emphasis added. The choice of the phrase "utility or usefulness" in the foregoing quotation is highly pertinent. The Federal Circuit is evidently using "utility" to refer to rejections under 35 U.S.C. § 101, and is using "usefulness" to refer to rejections under 35 U.S.C. § 112, first paragraph. This is made evident in the continuing text in *Brana*, which explains the correlation between 35 U.S.C. §§ 101 and 112, first paragraph. The Federal Circuit concluded:

> FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

Brana at 1442-1443, citations omitted. In assessing the question of whether undue experimentation would be required in order to practice the claimed invention, the key term is "undue", not "experimentation". *In re Angstadt and Griffin*, 190 USPQ 214 (C.C.P.A. 1976). The need for some experimentation does not render the claimed invention unpatentable. Indeed, a considerable amount of experimentation may be permissible if such experimentation is routinely practiced in the art. *In re Angstadt and Griffin, supra*; *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). As a matter of law, it is well settled that a patent need not disclose what is well known in the art. *In re Wands*, 8 USPQ 2d 1400 (Fed. Cir. 1988).

Finally, with regards to the issue of due process, while Appellants are well aware of the new Utility Guidelines set forth by the USPTO, Appellants respectfully point out that the current rules and regulations regarding the examination of patent applications is and always has been the patent laws as set forth in 35 U.S.C. and the patent rules as set forth in 37 C.F.R., not the Manual of Patent Examination Procedure or particular guidelines for patent examination set forth by the USPTO. Furthermore, it is the job of the judiciary, not the USPTO, to interpret these laws and rules. Appellants are unaware of any significant recent changes in either 35 U.S.C. § 101, or in the interpretation of 35 U.S.C. § 101 by the Supreme Court or the Federal Circuit that is in keeping with the new Utility Guidelines set forth by the USPTO. This is underscored by numerous patents that have been issued over the years that claim nucleic acid fragments that do not comply with the new Utility Guidelines. As examples of such issued U.S. Patents, the Board is invited to review U.S. Patent Nos. 5,817,479 (**Exhibit O**), 5,654,173 (**Exhibit P**), and 5,552,281 (**Exhibit Q**; each of which claims short polynucleotides), and recently issued U.S. Patent No. 6,340,583 (**Exhibit R**; which includes no working examples), none of which contain examples of the "real-world" utilities that the Examiner seems to be requiring. As issued U.S. Patents are presumed to meet all of the requirements for patentability, including 35 U.S.C. §§ 101 and 112, first paragraph (see Section VIII(B), below), Appellants submit that the present polynucleotides must also meet the requirements of 35 U.S.C. § 101. While Appellants agree that each application is examined on its own merits, Appellants are unaware of any changes to 35 U.S.C. § 101, or in the interpretation of 35 U.S.C. § 101 by the Supreme Court or the Federal Circuit, since the issuance of these patents that render the subject matter claimed in these patents, which is similar to the subject matter in question in the present application, as suddenly non-statutory or failing to meet the requirements of 35 U.S.C. § 101. Given the rapid pace of development in the biotechnology arts, it is difficult for the Appellants to understand how an invention fully disclosed and free of prior art at the time the present application was filed, could somehow retain *less* utility and be *less* enabled than inventions in the cited issued U.S. patents (which were filed during a time when the level of skill in the art was clearly lower). Simply put, Appellants invention is *more* enabled and retains *at least as much* utility as the inventions described in the claims of the U.S. patents of record. Thus, holding Appellants to a different

standard of utility would be arbitrary and capricious, and, like other clear violations of due process, cannot stand.

Thus in summary, Appellants have described novel nucleic and amino acid sequences, their tissue expression pattern and naturally occurring polymorphisms that exist within these molecules. Furthermore, the sequences of the present invention encode the human metalloprotease, neurolysin, a protein of well recognized function. In addition, Appellants have used methods described in the specification as filed to biologically validate their assertions that the sequences of the present invention have utility as drug targets for human disease. Thus, the conclusion reached from this analysis is that a 35 U.S.C. § 101 and a 35 U.S.C. § 112 first paragraph, utility rejection should not have been made. Therefore, Appellants respectfully submit that the rejection of the presently claimed invention under a 35 U.S.C. § 101 and a 35 U.S.C. § 112 first paragraph utility rejection should be overruled.

B. Are Claims 1-5 Unusable Due to a Lack of Patentable Utility?

The Final Action next rejects claims 1-5 under 35 U.S.C. § 112, first paragraph, since allegedly one skilled in the art would not know how to use the invention, as the invention allegedly is not supported by either a clear asserted utility or a well-established utility.

The arguments detailed above in **Section VIII(A)** concerning the utility of the presently claimed sequences are incorporated herein by reference. As the Federal Circuit and its predecessor have determined that the utility requirement of Section 101 and the how to use requirement of Section 112, first paragraph, have the same basis, specifically the disclosure of a credible utility (*In re Brana, supra*; *In re Jolles*, 628 F.2d 1322, 1326 n.11, 206 USPQ 885, 889 n.11 (CCPA 1980); *In re Fouche*, 439 F.2d 1237, 1243, 169 USPQ 429, 434 (CCPA 1971)), Appellants submit that as claims 1-5 have been shown to have "a specific, substantial, and credible utility", as detailed in **Section VIII(A)** above, the present rejection of claims 1-5 under 35 U.S.C. § 112, first paragraph, cannot stand.

Appellants therefore submit that the rejection of claims 1-5 under 35 U.S.C. § 112, first paragraph, must be overruled.

IX. APPENDIX

The claims involved in this appeal are as follows:

1. An isolated nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:1.

2. An isolated nucleic acid molecule comprising a nucleotide sequence that:

(a) encodes the amino acid sequence shown in SEQ ID NO: 2; and

(b) hybridizes under highly stringent conditions including washing in 0.1xSSC/0.1% SDS at 68°C to the nucleotide sequence of SEQ ID NO: 1 or the complement thereof.

3. An isolated nucleic acid molecule comprising a nucleotide sequence encoding the amino acid sequence shown in SEQ ID NO:2.

4. An expression vector comprising a nucleic acid sequence of Claim 3.

5. A cell comprising the expression vector of Claim 4.

X. CONCLUSION

Appellants respectfully submit that, in light of the foregoing arguments, the Final Action's conclusion that claims 1-5 lack a patentable utility and are unusable by the skilled artisan due to a lack of patentable utility is unwarranted. It is therefore requested that the Board overturn the Final Action's rejections.

Respectfully submitted,

September 29, 2003
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